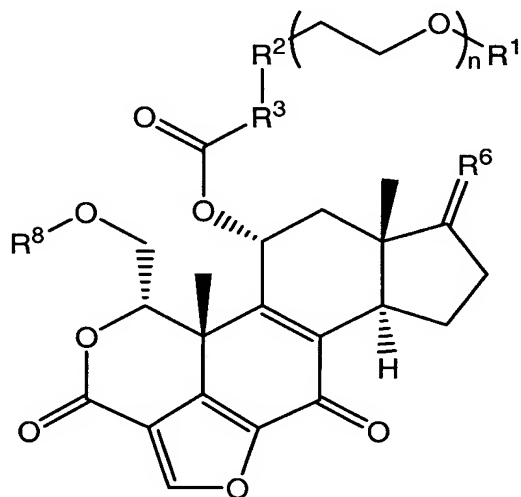


What is claimed is:

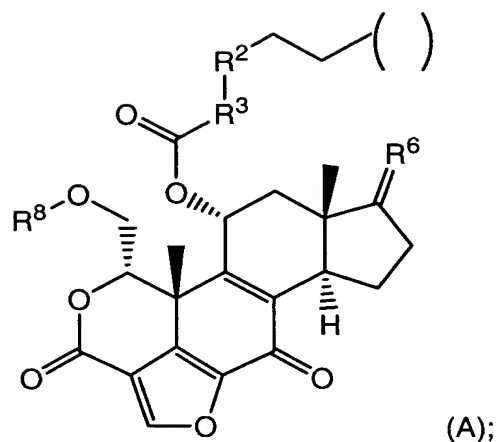
1. A water-soluble drug-polymer conjugate having the general formula P-X-D:  
  
wherein,  
  
5                   P is a water-soluble polymer;  
  
                  D is a wortmannin derivative; and  
  
                  X is a covalent linkage between a water-soluble polymer and the  
                  wortmannin derivative.
2. A pharmaceutical composition comprising the water-soluble drug-polymer  
10                   conjugate of claim 1 and a pharmaceutically acceptable carrier.
3. A method for treating or inhibiting a pathological condition or disorder  
                  mediated in a mammal comprising providing to said mammal an effective  
                  amount of a water-soluble drug-polymer conjugate of claim 1.
4. A method of claim 3 wherein the effective amount of the water-soluble drug-  
15                   polymer is 10 to 1000 mg/kg.
5. A method of claim 3 wherein the effective amount of the water-soluble drug-  
                  polymer is 0.5 to 10 mg/kg.
6. A method of claim 3 wherein treating or inhibiting comprises inhibition of PI3  
                  kinase.
- 20   7. A method of claim 3 wherein treating or inhibiting comprises inhibition of TOR  
                  kinase.
8. A method of claim 3 wherein the pathological condition is non-small cell lung  
                  cancer.

9. A method of claim 3 wherein the pathological condition is brain cancer, ischaemic heart disease, restenosis, inflammation, platelet aggregation, sclerosis, respiratory disorder, HIV and bone resorption.
10. A method of claim 3 wherein providing an effective amount is alone or in combination with other agents that modulate growth factor signaling, cytokine response, and cell cycle control.
11. A method of claim 10 wherein the agent is interferon- $\alpha$ .
12. A method of claim 10 wherein the agent is pegylated rapamycin.
13. A method of claim 10 wherein the agent is a cytotoxic.
14. A water-soluble drug-polymer conjugate having the structure of formula I



wherein:

$R^1$  is alkyl, or a drug-polymer conjugate of formula (A)



$R^2$  is -O-, -NH-, or -S-;

$R^3$  is alkyl, a cycloalkyl, or aryl;

$R^6$  is =O or  $OR^7$ ;

5  $R^7$  is H,  $COR^9$  or alkyl;

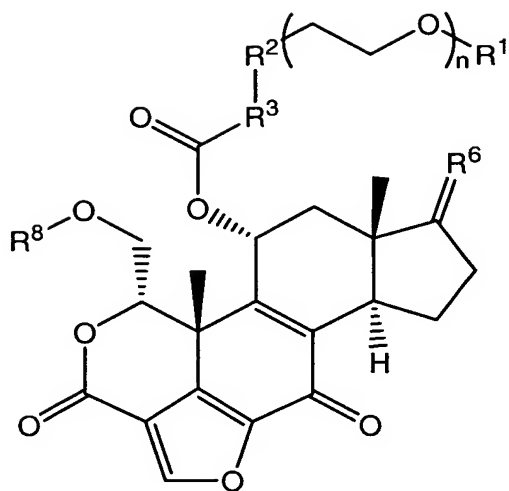
$R^8$  is alkyl or H;

$R^9$  is alkyl, H, aryl, or  $-CH_2Ar$ ; and

n is 1-1000.

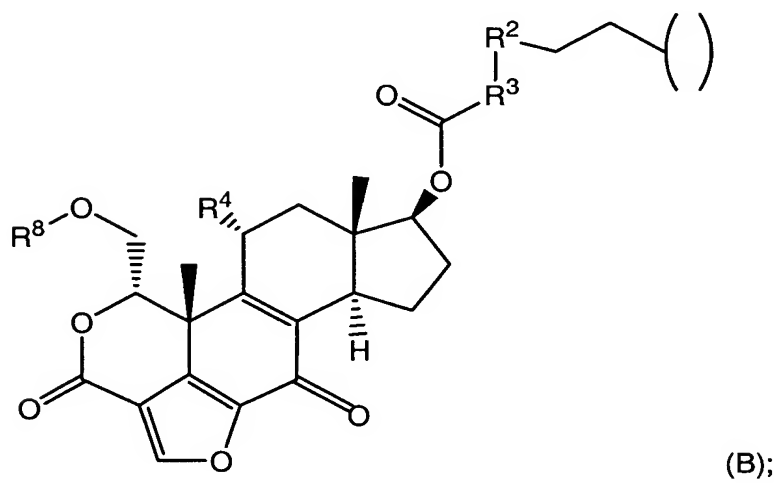
- 10 15. The water-soluble drug-polymer conjugate of claim 14 wherein n is 250 – 400.
16. The water-soluble drug-polymer conjugate of claim 14 wherein n is 50 – 150.
17. The water-soluble drug-polymer conjugate of claim 14 wherein the molecular weight of polymer is from about 400 to about 80,000.
- 15 18. The water-soluble drug-polymer conjugate of claim 14 wherein the molecular weight of polymer from about 1000 to about 8000.
19. The water-soluble drug-polymer conjugate of claim 14 wherein the molecular weight of polymer is from about 4000 to about 6000.

20. A pharmaceutical composition comprising the water-soluble drug-polymer conjugate of claim 14 and a pharmaceutically acceptable carrier.
21. A method for treating or inhibiting a pathological condition or disorder mediated in a mammal comprising providing to said mammal an effective amount of a water-soluble drug-polymer conjugate of claim 14.
22. A method of claim 21 wherein the effective amount of the water-soluble drug-polymer is 10 to 1000 mg/kg.
23. A method of claim 21 wherein the effective amount of the water-soluble drug-polymer is 0.5 to 10 mg/kg.
24. A method of claim 21 wherein treating or inhibiting comprises inhibition of PI3 kinase.
25. A method of claim 21 wherein treating or inhibiting comprises inhibition of TOR kinase.
26. A method of claim 21 wherein the pathological condition is non-small cell lung cancer.
27. A method of claim 21 wherein the pathological condition is brain cancer, ischaemic heart disease, restenosis, inflammation, platelet aggregation, sclerosis, respiratory disorder, HIV and bone resorption.
28. A method of claim 21 wherein providing an effective amount is alone or in combination with other agents that modulate growth factor signaling, cytokine response, and cell cycle control.
29. A method of claim 28 wherein the agent is interferon- $\alpha$ .
30. A method of claim 28 wherein the agent is pegylated rapamycin.
31. A method of claim 28 wherein the agent is a cytotoxic.
32. A water-soluble drug-polymer conjugate having the structure of formula I:



wherein:

$R^1$  is alkyl, or a drug-polymer conjugate of formula (B)



5

$R^2$  is -O-, -NH-, or -S-;

$R^3$  is alkyl, a cycloalkyl, or aryl;

$R^4$  is H, =O, -O-COC<sub>4</sub>H<sub>9</sub>, or OR<sup>7</sup>;

$R^7$  is H, COR<sup>9</sup> or alkyl;

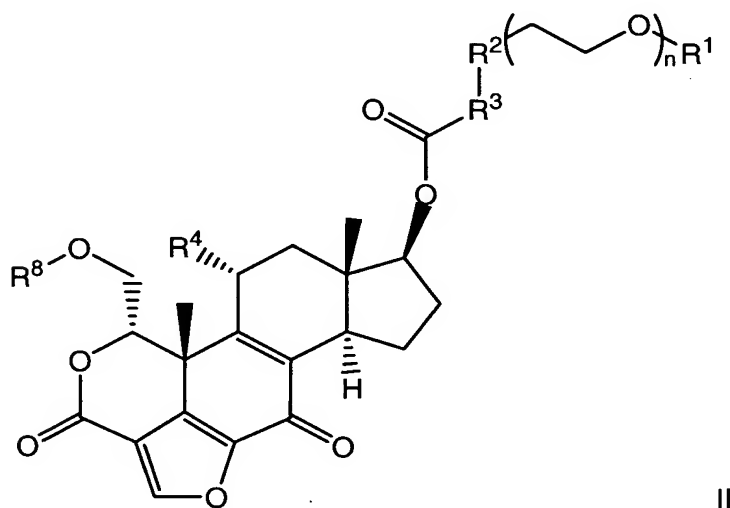
$R^8$  is alkyl or H;

$R^9$  is alkyl, H, aryl, or  $-\text{CH}_2\text{Ar}$ ; and

n is 1-1000.

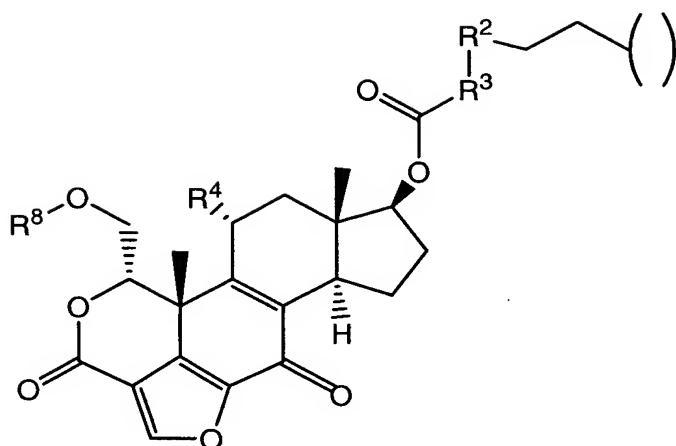
33. The water-soluble drug-polymer conjugate of claim 32 wherein n is 250 – 400.
- 5 34. The water-soluble drug-polymer conjugate of claim 32 wherein n is 50 – 150.
35. The water-soluble drug-polymer conjugate of claim 32 wherein the molecular weight of polymer is from about 400 to about 80,000.
36. The water-soluble drug-polymer conjugate of claim 32 wherein the molecular weight of polymer is from about 1000 to about 8000.
- 10 37. The water-soluble drug-polymer conjugate of claim 32 wherein the molecular weight of polymer is from about 4000 to about 6000.
38. A pharmaceutical composition comprising the water-soluble drug-polymer conjugate of claim 32 and a pharmaceutically acceptable carrier.
- 15 39. A method for treating or inhibiting a pathological condition or disorder mediated in a mammal comprising providing to said mammal an effective amount of a water-soluble drug-polymer conjugate of claim 32.
40. A method of claim 39 wherein the effective amount of the water-soluble drug-polymer is 10 to 1000 mg/kg.
- 20 41. A method of claim 39 wherein the effective amount of the water-soluble drug-polymer is 0.5 to 10 mg/kg.
42. A method of claim 39 wherein treating or inhibiting comprises inhibition of PI3 kinase.
43. A method of claim 39 wherein treating or inhibiting comprises inhibition of TOR kinase.

44. A method of claim 39 wherein the pathological condition is non-small cell lung cancer.
45. A method of claim 39 wherein the pathological condition is brain cancer, ischaemic heart disease, restenosis, inflammation, platelet aggregation, sclerosis, respiratory disorder, HIV and bone resorption.
46. A method of claim 39 wherein providing an effective amount is alone or in combination with other agents that modulate growth factor signaling, cytokine response, and cell cycle control.
47. A method of claim 46 wherein the agent is interferon- $\alpha$ .
48. A method of claim 46 wherein the agent is pegylated rapamycin.
49. A method of claim 46 wherein the agent is a cytotoxic.
50. A water-soluble drug-polymer conjugate having the structure of formula II



wherein:

- $R^1$  is alkyl, or a drug-polymer conjugate of formula (B)



(B);

$R^2$  is -O-, -NH-, or -S-;

$R^3$  is alkyl, a cycloalkyl, or aryl;

$R^4$  is H, =O, -O-COC<sub>4</sub>H<sub>9</sub>, or OR<sup>7</sup>;

5  $R^7$  is H, COR<sup>9</sup> or alkyl;

$R^8$  is alkyl or H;

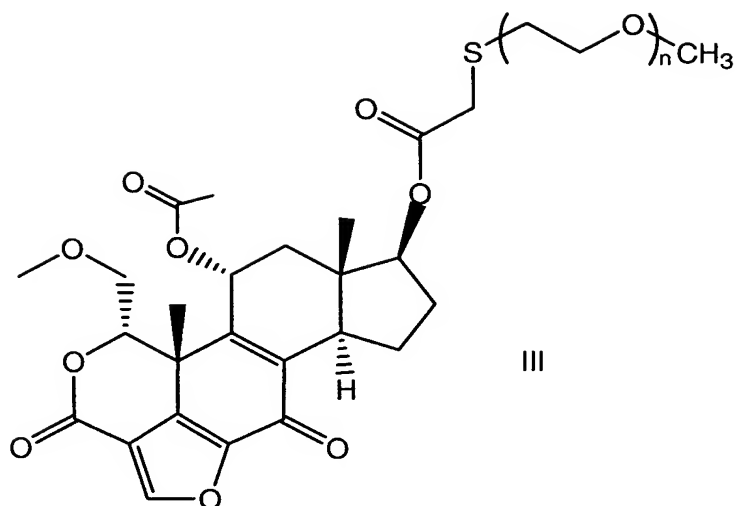
$R^9$  is alkyl, H, aryl, or -CH<sub>2</sub>Ar; and

n is 1-1000.

- 10 51. The water-soluble drug-polymer conjugate of claim 50 wherein n is 250 – 400.
52. The water-soluble drug-polymer conjugate of claim 50 wherein n is 50 – 150.
53. The water-soluble drug-polymer conjugate of claim 50 wherein the molecular weight of polymer is from about 400 to about 80,000.
- 15 54. The water-soluble drug-polymer conjugate of claim 50 wherein the molecular weight of polymer is from about 1000 to about 8000.
55. The water-soluble drug-polymer conjugate of claim 50 wherein the molecular weight of polymer is from about 4000 to about 6000.

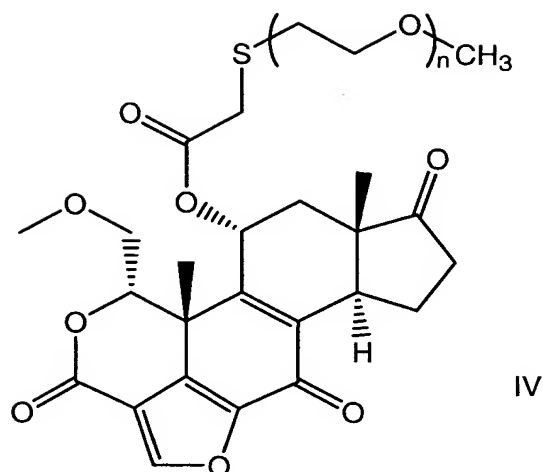


56. A pharmaceutical composition comprising the water-soluble drug-polymer conjugate of claim 50 and a pharmaceutically acceptable carrier.
57. A method for treating or inhibiting a pathological condition or disorder mediated in a mammal comprising providing to said mammal an effective amount of a water-soluble drug-polymer conjugate of claim 50.
58. A method of claim 57 wherein the effective amount of the water-soluble drug-polymer is 10 to 1000 mg/kg.
59. A method of claim 57 wherein the effective amount of the water-soluble drug-polymer is 0.5 to 10 mg/kg.
60. A method of claim 57 wherein treating or inhibiting comprises inhibition of PI3 kinase.
61. A method of claim 57 wherein treating or inhibiting comprises inhibition of TOR kinase.
62. A method of claim 57 wherein the pathological condition is non-small cell lung cancer.
63. A method of claim 57 wherein the pathological condition is brain cancer, ischaemic heart disease, restenosis, inflammation, platelet aggregation, sclerosis, respiratory disorder, HIV and bone resorption.
64. A method of claim 57 wherein providing an effective amount is alone or in combination with other agents that modulate growth factor signaling, cytokine response, and cell cycle control.
65. A method of claim 64 wherein the agent is interferon- $\alpha$ .
66. A method of claim 64 wherein the agent is pegylated rapamycin.
67. A method of claim 64 wherein the agent is a cytotoxic.
68. A water-soluble drug-polymer conjugate having the structure of formula III:



n is 1-1000.

69. The water-soluble drug-polymer conjugate of claim 68 wherein n is 250 – 400.
- 5 70. The water-soluble drug-polymer conjugate of claim 68 wherein n is 50 – 150.
71. The water-soluble drug-polymer conjugate of claim 68 wherein the molecular weight of polymer is from about 400 to about 80,000.
72. The water-soluble drug-polymer conjugate of claim 68 wherein the molecular weight of polymer is from about 1000 to about 8000.
- 10 73. The water-soluble drug-polymer conjugate of claim 68 wherein the molecular weight of polymer is from about 4000 to about 6000.
74. A water-soluble drug-polymer conjugate having the structure of formula IV:



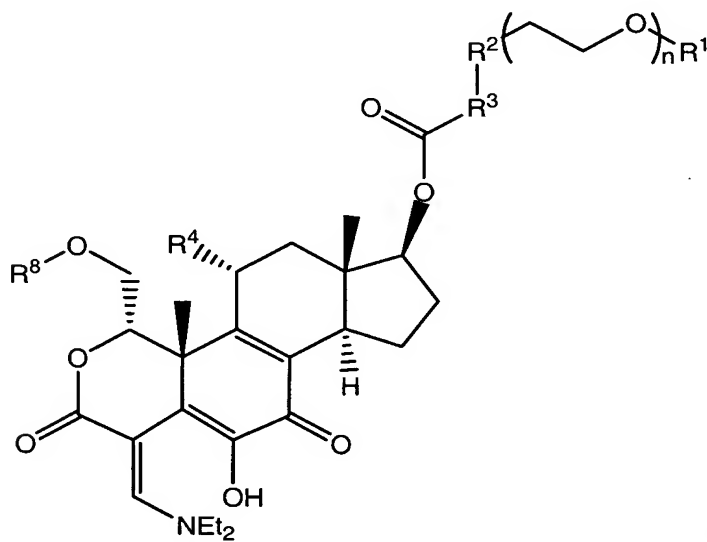
wherein  $n = 1-1000$ .

75. The water-soluble drug-polymer conjugate of claim 74 wherein  $n$  is 250 – 400.
- 5 76. The water-soluble drug-polymer conjugate of claim 74 wherein  $n$  is 50 – 150.
77. The water-soluble drug-polymer conjugate of claim 74 wherein the molecular weight of polymer is from about 400 to about 80,000.
78. The water-soluble drug-polymer conjugate of claim 74 wherein the molecular weight of polymer is from about 1000 to about 8000.
- 10 79. The water-soluble drug-polymer conjugate of claim 74 wherein the molecular weight of polymer is from about 4000 to about 6000.
80. A pharmaceutical composition comprising the water-soluble drug-polymer conjugate of claim 74 and a pharmaceutically acceptable carrier.
81. A method for treating or inhibiting a pathological condition or disorder mediated in a mammal comprising providing to said mammal an effective amount of a water-soluble drug-polymer conjugate of claim 74.
- 15 82. A method of claim 81 wherein the effective amount of the water-soluble drug-polymer is 10 to 1000 mg/kg.

- 83. A method of claim 81 wherein the effective amount of the water-soluble drug-polymer is 0.5 to 10 mg/kg.
- 84. A method of claim 81 wherein treating or inhibiting comprises inhibition of PI3 kinase.
- 5 85. A method of claim 81 wherein treating or inhibiting comprises inhibition of TOR kinase.
- 86. A method of claim 81 wherein the pathological condition is non-small cell lung cancer.
- 10 87. A method of claim 81 wherein the pathological condition is brain cancer, ischaemic heart disease, restenosis, inflammation, platelet aggregation, sclerosis, respiratory disorder, HIV and bone resorption.
- 88. A method of claim 81 wherein providing an effective amount is alone or in combination with other agents that modulate growth factor signaling, cytokine response, and cell cycle control.
- 15 89. A method of claim 88 wherein the agent is interferon- $\alpha$ .
- 90. A method of claim 88 wherein the agent is pegylated rapamycin.
- 91. A method of claim 88 wherein the agent is a cytotoxic.
- 92. A process for the preparation of a water-soluble drug-polymer conjugate of claim 68 comprising:
  - 20 a. adding a solvent to 17-dihydro-17-(1-iodoacetyl)-wortmannin to obtain a solution;
  - b. adding a tertiary amine or sodium bicarbonate to the solution;
  - c. adding mPEG-sulfhydryl 5000 to the solution of step (b);
  - d. stirring the solution of step (c) for 30 minutes;

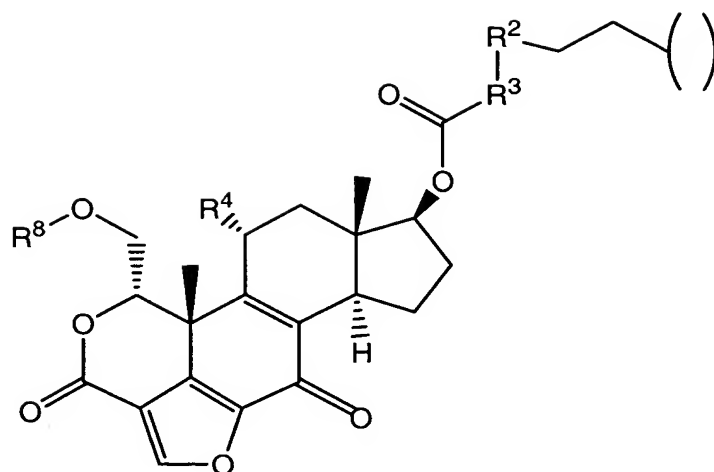
- e. adding ether to the stirred solution;
- f. collecting the solid; and
- g. washing the collected solid with ether to obtain the pegylated wortmannin derivative.

5 93. A water-soluble drug-polymer conjugate having the structure of formula V:



wherein:

$R^1$  is alkyl, or a drug-polymer conjugate of a single non-repeating formula (V)



$R^2$  is -O-, -NH-, or -S-;

$R^3$  is alkyl, a cycloalkyl, or aryl;

$R^4$  is H, =O, -O-COC<sub>4</sub>H<sub>9</sub>, or OR<sup>7</sup>;

5  $R^7$  is H, COR<sup>9</sup> or alkyl;

$R^8$  is alkyl or H;

$R^9$  is alkyl, H, aryl, or -CH<sub>2</sub>Ar; and

$n$  is 1-1000.

- 10 94. A process for the preparation of the compound of claim 93 comprising addition of an amine to a compound of claim 50 to obtain a compound of claim 93.
95. A process of claim 94 wherein the amine comprises diethyl amine.
96. A process for the preparation of a water-soluble drug-polymer conjugate of claim 74 comprising:
- 15 a) adding a solvent to 11-desacetyl-11-(1-iodoacetyl)-wortmannin to obtain a solution;

- b) adding a tertiary amine to the solution;
  - c) adding mPEG-sulfhydryl 5000 to the solution of step (b);
  - d) stirring the solution of step (c) for 30 minutes;
  - e) adding ether to the stirred solution;
  - 5 f) collecting the solid; and
  - g) washing the collected solid with ether to obtain the pegylated wortmannin derivative,
- as disclosed.